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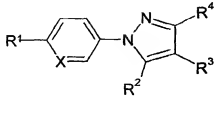
(54) Title: PYRAZOLE DERIVATIVES

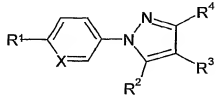


(I)

(57) Abstract: Compounds of the formula (I) and salts and solvates thereof, in which X, R^1, R^2, R^3, R^4 and R^5 are as defined in Claim 1, are suitable as glycine transporter inhibitors and can be used in human and veterinary medicine for the prophylaxis and treatment of schizophrenia, depression, dementia, Parkinson's disease, Alzheimer's disease, Lewy bodies dementia, Huntington's disease, Tourette's syndrome, anxiety, learning and memory restrictions, neurodegenerative disorders and other cognitive impairments, as well as nicotine dependence and pain.

PYRAZOLE DERIVATIVES AS GLYCINE TRANSPORTE INHIBITORS

The invention relates to compounds of the formula I



I

in which

X is CH or N,

R^1 is H, A, Hal, $(CH_2)_nHet$, $(CH_2)_nAr$, cycloalkyl having from 3 to 7 carbon atoms, CF_3, NO_2, CN, C(NH)NOH or OCF_3,

R^2 is $(CH_2)_nHet$, $(CH_2)_nAr$, cycloalkyl having from 3 to 7 carbon atoms or CF_3,

R^3 and R^4 are H, $(CH_2)_nCO_2R^5$, $(CH_2)_nCOHet$, $(CH_2)_nCOO(CH_2)_nHet$, CHO, $(CH_2)_nOR^5$, $(CH_2)_nHet$, $(CH_2)_nN(R^5)_2$, CH=N-OA, CH_2CH=N-OA, $(CH_2)_nNHOA$, $(CH_2)_nN(R^5)Het$, $(CH_2)_nCH$=N-Het, $(CH_2)_nOCOR^5$, $(CH_2)_nN(R^5)CH_2CH_2OR^5$, $(CH_2)_nN(R^5)CH_2CH_2OCF_3$, $(CH_2)_nN(R^5)C(R^5)HCOOR^5$, $(CH_2)_nN(R^5)CH_2COHet$, $(CH_2)_nN(R^5)CH_2Het$, $(CH_2)_nN(R^5)CH_2CH_2Het$, $(CH_2)_nN(R^5)CH_2CH_2N(R^5)CH_2COOR^5$, $(CH_2)_nN(R^5)CH_2CH_2N(R^5)_2$, CH=$CHCOOR^5$, CH=$CHCH_2NR^5Het$, CH=$CHCH_2N(R^5)_2$, CH=$CHCH_2OR^5$, $(CH_2)_nN(R^5)Ar$, $(CH_2)_nN(COOR^5)COOR^5$, $(CH_2)_nN(CONH_2)COOR^5$, $(CH_2)_nN(CONH_2)CONH_2$, $(CH_2)_nN(CH_2COOR^5)COOR^5$, $(CH_2)_nN(CH_2CONH_2)COOR^5$, $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^5COR^5$, $(CH_2)_nCHR^5COOR^5$ or $(CH_2)_nCHR^5CH_2OR^5$, where in each case one of the radicals R^3 or R^4 is H,

R^5 is H or A,

A is straight-chain or branched alkyl having from 1 to 10 carbon atoms, alkenyl having from 2 to 10 carbon atoms or alkoxyalkyl having from 2 to 10 carbon atoms,

Het is a saturated, unsaturated or aromatic monocyclic or bicyclic heterocyclic radical which is unsubstituted or monosubstituted or polysubstituted by A and/or Hal,

Ar is a phenyl radical which is unsubstituted or monosubstituted or polysubstituted by A and/or Hal, OR^5, $OOCR^5$, $COOR^5$, $CON(R^5)_2$, CN, NO_2, NH_2, $NHCOR^5$, CF_3 or SO_2CH_3,

n is 0, 1, 2, 3, 4 or 5,

and

Hal is F, Cl, Br or I,

and salts and solvates thereof, in particular physiologically tolerated salts and solvates thereof,

where compounds of the formula I in which R^1 and R^4 are H, X is CH_2, R^2 is phenyl or p-chlorophenyl, and R^3 is 1-methyl-4-piperidyloxycarbonyl, 2-(4-phenylpiperazino)ethoxycarbonyl, benzoxazol-2-yl, benzothiazol-2-yl, tetrazol-5-yl or unsubstituted or substituted thiazolidin-2-yl, and salts and solvates thereof, are excluded.

The invention had the object of finding novel compounds having valuable properties, in particular those which can be used for the preparation of medicaments.

It has been found that the compounds of the formula I and their salts and solvates have very valuable pharmacological properties and are well tolerated.

Similar compounds are disclosed, for example, in DE 2201889, DE 2258033 and DE 2906252.

In particular, the compounds of the formula I according to the invention are suitable as glycine transporter inhibitors and can be used in human and veterinary medicine for the prophylaxis and treatment of schizophrenia, depression, dementia, Parkinson's disease, Alzheimer's disease, Lewy bodies dementia, Huntington's disease, Tourette's syndrome, anxiety, learning and memory restrictions, neurodegenerative disorders and other cognitive impairments, as well as nicotine dependence and pain.

Glycine is known as an excitatory and inhibitory neurotransmitter of the central and peripheral nervous system. These functions are exerted via two different types of receptor, with different types of glycine transporters being involved in each case in regulation of neuronal transmission.

The function as inhibitory neurotransmitter acts via the strychnine-sensitive glycine receptor, which occurs predominantly in the spinal cord and in the brain stem.
On the other hand, the excitatory function is exerted via the N-methyl-D-aspartic acid (NMDA) receptor, which is a sub-type of the glutamate receptors and is widespread in the brain, in particular in the cerebral cortex and the hippocampus.
Glycine acts here as coagonist on the NMDA receptor (Johnson, J.W., Asher, P., Nature, 325, 529-531. (1987)).

Neurotransmitter transporters play an important role in control of the concentration of neurotransmitters in the synaptic cleft, with the transmitters being taken up by the cells. It is assumed that neurotransmitter transporters also contribute to recycling of the neurotransmitters in that the neurotransmitters are taken up by the pre-synaptic nerve endings.

Control of the functions of the neurotransmitters can make a significant contribution towards therapeutic treatment of various illnesses caused by dysfunction of the neural functions, where mention should also be made of control of the concentration of the neurotransmitter in the synaptic cleft.

The glycine transporter (GLYT) was cloned for the first time in 1992 (Guastella, J. et al., Proc. Natl. Acad. Sci., 89, 7189-93, 1992). Two types of these transporters, GLYT1 and GLYT2, have been identified to date (Liu, Q.R. et al., J. Biol. Chem., 268, 22802-8, 1993).
GLYT1 has numerous splicing variants (Kim, K.M. et al., Mol. Pharmacol., 45, 608-17, 1994) and is expressed predominantly in the spinal cord, brain stem, cerebellum, diencephalon and in the retina, while it is expressed to a smaller extent in the bulbus olfactorius and the cerebrum halves.
It is assumed that GLYT1 is involved in control of the NMDA receptor function (Smith, K.E. et al., Neuron, 8, 927-35; Guastella, J. et al., Proc. Natl. Acad. Sci, 89, 7189-93, 1992; Bergeron, R. et al., Proc. Natl. Acad. Sci. USA, 95, 15730-15734, 1998)

It is furthermore known that the glycine transporter inhibitor glycyldodecylamide (GDA) inhibits hyperactivity in mice caused by the non-competitive NMDA receptor antagonist phencylidine (PCP) (Javitt, D.C. et al., Neuropsychopharmacology, 17, 202-4, 1997)

The expression of GLYT2 is limited to the spinal cord, the brain stem and the cerebellum (Goebel, D.J., Mol. Brain Res., 40, 139-42, 1996; Zafra, F. et al., J. Neurosci., 15, 3952-69, 1995). It is therefore assumed that GLYT2 is involved in control of the function of the strychnine-sensitive glycine receptor. It is assumed that the inhibition of GLYT2 reduces the transmission of pain in the spinal cord through the reinforcing action of the strychnine-sensitive glycine transporter function (Yaksh, T. L., Pain, 37, 111-123, 1989).

The reinforcement of the strychnine-sensitive glycine receptor function can be employed in the therapeutic treatment of abnormal muscle contraction, such as, for example, cramps, myoclonia and epilepsy (Truong, D.D. et al., Movement Disorders, 3, 77-87, 1988; Becker, C.M. et al., FASEB J. 4, 2767-2774, 1990).
Cramps are associated with nerve disorders and damage, as occur in epilepsy, disorders of the cerebral blood vessel system, head injuries, multiple sclerosis, damage to the spinal cord and dystonia.

It is known that the NMDA receptor is involved in various syndromes. Thus, it is thought that the functional weakening of the NMDA receptor plays a role in schizophrenia (Javitt, D.C., Zukin, S.R., American Journal of Psychiatry, 148, 1301-8, 1991).
Furthermore, it is claimed that the negative symptoms in schizophrenia patients can be ameliorated by administration of high doses of glycine (Heresco-Levy, U. et al., Br. J. Psychiatry, 169, 610-7, 1996).
Furthermore, activation of the NMDA receptor is involved in the formation of so-called long-term potentiation (LTP) (Collingridge, G.L. , Bliss T.V., Trends. Neurosci., 10, 288-93, 1987).

Morris et al. have observed that the administration of an NMDA receptor antagonist induces a memory disorder (Morris, R.G. et al., Nature, 319, 774-6, 1986, Benvenga, M. Theodore, C.S. Pharmacol. Biochem. Behav., 30, 205-207, 1988). It is thus assumed that the NMDA receptor plays an important role in the memory and learning process.

In patients with Alzheimer's-type dementia, an impairment in the function of the NMDA receptors has been observed (Ninomiya, H. et al., J. Neurochem., 54, 526-32, 1990; Tohgi, H. et al. Neurosci. Lett., 141, 5-8, 1992).

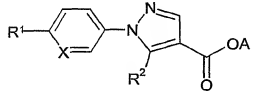
Furthermore, a number of articles have reported that a memory disorder can be countered by administration of a "glycine site" agonist in an animal model (Matsuoka, N., Aigner, T.G., J. Exp. Pharmacol. Ther., 278, 891-7, 1996; Ohno, M. et al. J. Pharmacol., 253, 183-7, 1994; Fishkin, J.J. et al., Behav. Neural. Biol., 59, 150-7, 1993).
These results confirm that active ingredients which inhibit the activity of the glycine transporters and activate the function of the NMDA receptor via the associated increased glycine concentration can be used in human and veterinary medicine, in particular for the prophylaxis and treatment of schizophrenia, depression, dementia, Parkinson's disease, Alzheimer's disease, Lewy bodies dementia, Huntington's disease, Tourette's syndrome, anxiety, learning and memory restrictions, neurodegenerative disorders and other cognitive impairments, as well as nicotine dependence and pain.

Various compounds have already been disclosed as glycine transporter inhibitors. Thus, WO 97/45115 mentions tertiary amines, WO 97/45423 mentions pyrimidine derivatives, WO 99/34790 mentions amino acid derivatives, WO 99/41227 mentions tricyclic compounds, WO 99/44596 and WO 99/45011 mention piperidine derivatives and WO 00/07978 mentions aminomethylcarboxylic acid derivatives in addition to glycyldodecylamide (GDA) as glycine transporter inhibitors.

However, none of the above-mentioned documents describes the compounds of the formula I or the use of the compounds of the formula I according to the invention as glycine transporter inhibitors.

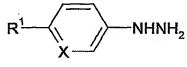
The compounds of the formula I can be employed as medicament active ingredients in human and veterinary medicine. They can furthermore be employed as intermediates for the preparation of further medicament active ingredients.

The invention accordingly relates to the compounds of the formula I and to the use thereof in human and animal medicine.
The present invention furthermore relates to a process for the preparation of compounds of the formula IA



IA

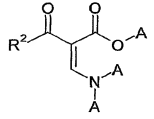
and salts and solvates thereof, which is characterised in that a compound of the formula II



II

or acid-addition salts thereof

in which
R^1 and X are as defined above,
is reacted with a compound of the formula III

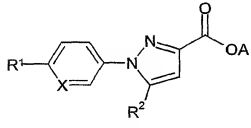


III

in which
A and R^2 are as defined above,

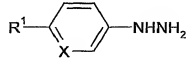
and/or in that a basic compound of the formula IA is converted into one of its salts by treatment with an acid.

The present invention furthermore relates to a process for the preparation of compounds of the formula IB



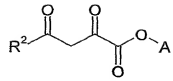
IB

and salts and solvates thereof, which is characterised in that a compound of the formula II



II

or acid-addition salts thereof
in which
R^1 and X are as defined above,
is reacted with a compound of the formula IV

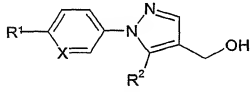


IV

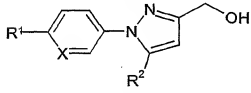
in which
A and R^2 are as defined above,

and/or in that a basic compound of the formula IB is converted into one of its salts by treatment with an acid.

The compounds of the formulae IA and IB can be converted into further compounds of the formula I by conventional methods. In particular, the compounds of the formulae IA and IB can be converted, using reducing agents, such as, for example, lithium aluminium hydride, into the corresponding alcohols of the formulae IC and ID

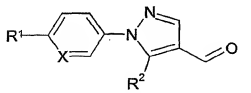


IC

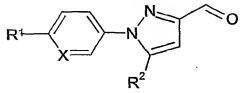


ID

which can be oxidised, for example using MnO_2, to give the compounds IE and IF

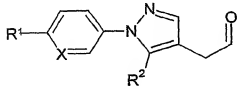


IE

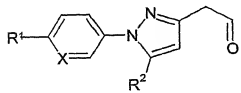


IF

The compounds of the formulae IE and IF can themselves be aminated by known methods using corresponding nucleophiles, such as, for example, nitrogen bases, in particular hydroxylamine, O-methylhydroxylamine, morpholine, piperidine, piperazine, N-methylpiperazine, 4-methylpiperazin-1-ylamine, pyrrolidine, pyrazolidine or imidazolidine, if desired in the presence of a reducing agent, such as sodium triacetoxyborohydride, or converted into the corresponding imines. Furthermore, the compounds of the formulae IE and IF can be converted, by Wittig reaction with methoxymethyltriphenylphosphonium salts, into the corresponding enol ethers, which can be converted, by treatment with an acid, into the homologous aldehydes IG and IH



IG



IH

The compounds of the formulae IG and IH can be converted into further compounds of the formula I analogously to the compounds of the formulae IE and IF.

The invention likewise relates to the novel compounds of the formulae II, III, IV and V.

The term solvates of the compounds of the formula I is taken to mean adductions of inert solvent molecules onto the compounds of the formula I which form owing to their mutual attractive force. Solvates are, for example, mono- or dihydrates or alcoholates.

Above and below, the radicals X, A, Ar, Het, n, R^1, R^2, R^3, R^4 and R^5 are as defined for the formula I, unless expressly stated otherwise.

X is preferably N.

R^1 is preferably A, Hal, $(CH_2)_nHet$ or $(CH_2)_nAr$, in particular A, $(CH_2)_nHet$ or $(CH_2)_nAr$. R^1 is very particularly preferably phenyl, 2-, 3- or 4-cyanophenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-methyl-, -ethyl-, -n-propyl- or -n-butyl-phenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, 3,5- or 3,6-difluoro-, -dichloro- or -dicyanophenyl, 3,4,5-trifluorophenyl, 3,4,5-trimethoxy- or -triethoxyphenyl, thiophen-2-yl or thiophen-3-yl.

R^2 is preferably $(CH_2)_nHet$ or $(CH_2)_nAr$, in particular $(CH_2)_nAr$. R^2 is very particularly preferably phenyl, 2-, 3- or 4-cyanophenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-methyl-, -ethyl-, -n-propyl- or -n-butylphenyl, 2,3-, 2,4-, 2,5- or 2,6-difluoro- or -dicyanophenyl, thiophen-2-yl or thiophen-3-yl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, quinolinyl, isoquinolinyl, 2- or 4-pyridazyl, 2-, 4- or 5-pyrimidyl, or 2- or 3-pyrazinyl.

If R^3 is H, R^4 is preferably $(CH_2)_nCO_2R^5$, $(CH_2)_nCO$-Het, CHO, CH_2OR^5, $(CH_2)_n$-Het, $(CH_2)_nN(R^5)_2$ or CH=N-OA, but in particular $(CH_2)_nCO_2R^5$, $(CH_2)_nCO$-Het, CHO, CH=N-OA or $(CH_2)_n$-Het. If R^4 is H, R^3 is preferably $(CH_2)_nCO_2R^5$, $(CH_2)_nCO$-Het, CHO, CH_2OR^5, $(CH_2)_n$-Het, $(CH_2)_nN(R^5)_2$ or CH=N-OA, but in particular $(CH_2)_nCO_2R^5$, $(CH_2)_nCO$-Het, CHO, CH=N-OA or $(CH_2)_n$-Het. R^4 is particularly preferably H.

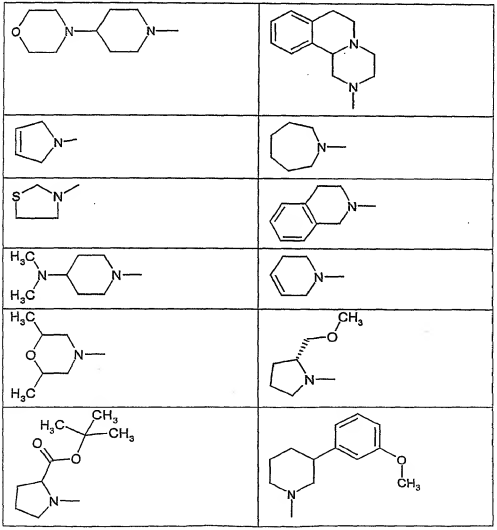
R^5 is preferably A.

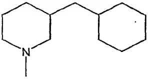
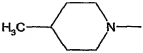
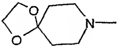
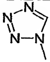
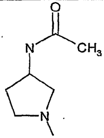
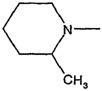
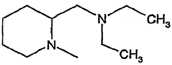
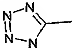
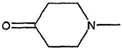
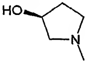
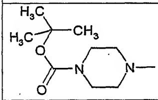
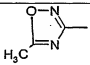
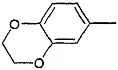
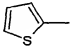
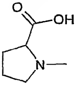
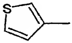
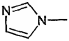
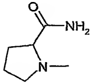
A is preferably alkyl, is preferably unbranched and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, preferably 1, 2, 3, 4, 5 or 6 carbon atoms, and is preferably methyl, ethyl, n-propyl, furthermore preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also n-pentyl, neopentyl, isopentyl or n-hexyl. Particular preference is given to methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl or n-decyl.

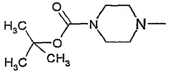
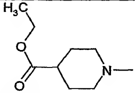
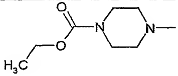
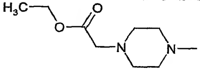
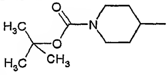
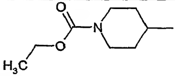
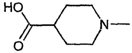
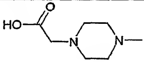
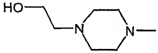
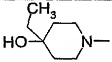
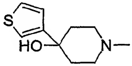
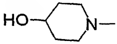
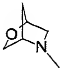
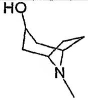
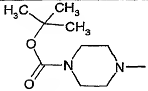
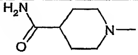
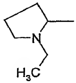
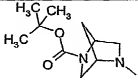
A is furthermore preferably the $(CH_2)_mOCH_3$ or $(CH_2)_mC_2H_5$ group, in which m is 2, 3, 4, 5 or 6, but in particular 2.

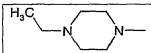
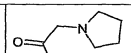
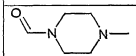
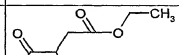
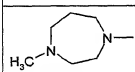
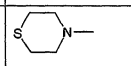
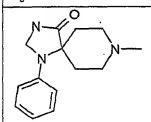
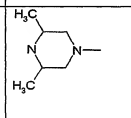
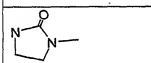
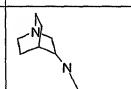
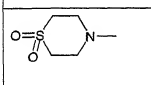
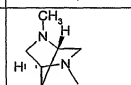
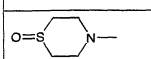
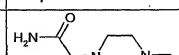
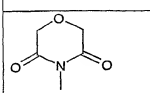
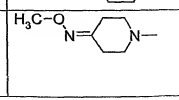
If A is alkenyl, it is preferably allyl, 2- or 3-butenyl, isobutenyl, sec-butenyl, furthermore preferably 4-pentenyl, isopentenyl or 5-hexenyl.

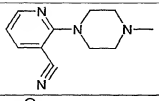
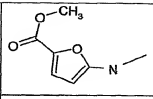
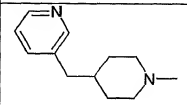
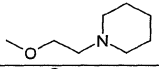
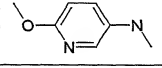
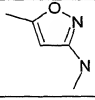
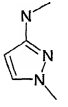
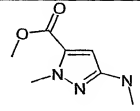
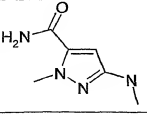
Het is preferably an aromatic or in particular saturated heterocyclic radical which is unsubstituted or substituted by A. Het is preferably 1-piperidyl, 1-piperazyl, 1-(4-methyl)piperazyl, 4-methylpiperazin-1-ylamine, 4-morpholinyl, 1-pyrrolidinyl, 1-pyrazolidinyl, 1-(2-methyl)pyrazolidinyl, 1-imidazolidinyl or 1-(3-methyl)imidazolidinyl, thiophen-2-yl or thiophen-3-yl, 2-, 3- or 4-pyridyl, which may be unsubstituted or substituted by one or more CN groups, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, quinolinyl, isoquinolinyl, 2- or 4-pyridazyl, 2-, 4- or 5-pyrimidyl, or 2- or 3-pyrazinyl. Het is furthermore preferably a radical from the following table:

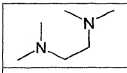
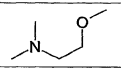
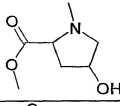
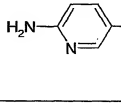
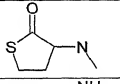
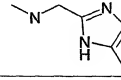
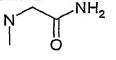
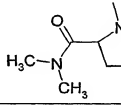
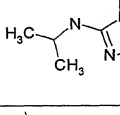
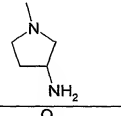
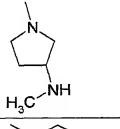
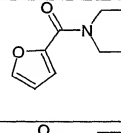
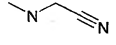
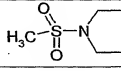
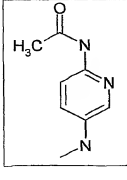
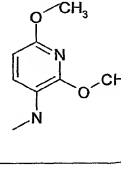


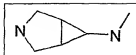
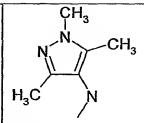
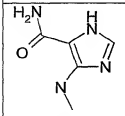
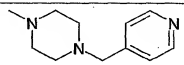
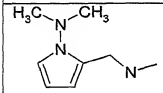
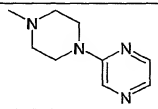
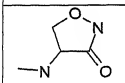
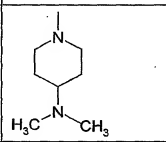
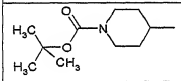
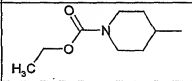
	
	
	
	
	
	
	
	
	

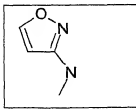
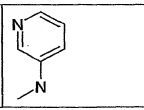
	
	
	
	
	
	
	
	

Het is particularly preferably one of the following radicals:

Ar is preferably a phenyl radical which is unsubstituted or substituted by Hal, OH, CN, NO_3, NH_2, $NHCOCH_3$, $COOCH_3$, $CONH_2$ or CF_3. Ar is preferably substituted in the 4- or 3-position.

n is preferably 0, 1 or 2, in particular 0 or 1.

Cycloalkyl preferably has 3-7 carbon atoms and is preferably cyclopropyl or cyclobutyl, furthermore preferably cyclopentyl or cyclohexyl, furthermore also cycloheptyl, particularly preferably cyclopentyl.

Hal is preferably F, Cl or Br, but also I.

If the compounds of the formula I have one or more chiral carbon atoms, the present invention relates to the enantiomers, diastereomers and mixtures thereof.

Throughout the invention, all radicals which occur more than once may be identical or different, i.e. are independent of one another.

Accordingly, the invention relates, in particular, to the compounds of the formula I in which at least one of the radicals mentioned has one of the preferred meanings indicated above. Some preferred groups of compounds may be expressed by the following sub-formulae I1 to I9, which conform to the formula I and in which the radicals not designated in greater detail are as defined for the formula I, but in which

in I1 R^1 is $(CH_2)_nHet$ or $(CH_2)_nAr$;

in I2 R^1 is $(CH_2)_nHet$ or $(CH_2)_nAr$,
R^2 is $(CH_2)_nAr$;

in I3 R^1 is $(CH_2)_nAr$,
R^2 is $(CH_2)_nAr$;

in I4 R^1 is $(CH_2)_nHet$ or $(CH_2)_nAr$,
R^2 is $(CH_2)_nAr$,
R^4 is H,
R^3 is $(CH_2)_nCO_2R^5$, $(CH_2)_nCO$-Het, CHO, CH_2OR^5, $(CH_2)_n$-Het, $(CH_2)_nN(R^5)_2$ or CH=N-OA;

in I5 R^1 is $(CH_2)_nHet$ or $(CH_2)_nAr$,
R^2 is $(CH_2)_nAr$,
R^4 is H,
R^3 is $(CH_2)_nCO_2R^5$, $(CH_2)_nCO$-Het, CHO, CH_2OR^5, $(CH_2)_n$-Het, $(CH_2)_nN(R^5)_2$ or CH=N-OA,
R^5 is H, methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl or n-decyl;

in I6 R^1 is $(CH_2)_nHet$ or $(CH_2)_nAr$,
R^2 is $(CH_2)_nAr$,
R^4 is H,
R^3 is $(CH_2)_nCO_2R^5$, $(CH_2)_nCO$-Het, CHO, CH_2OR^5, $(CH_2)_n$-Het, $(CH_2)_nN(R^5)_2$ or CH=N-OA,
R^5 is H, methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl or n-decyl,
n is 0, 1 or 2;

in I7 R^1 is $(CH_2)_nHet$ or $(CH_2)_nAr$,
R^2 is $(CH_2)_nAr$,
R^3 is H,
R^4 is $(CH_2)_nCO_2R^5$, $(CH_2)_nCO$-Het, CHO, CH_2OR^5, $(CH_2)_n$-Het, $(CH_2)_nN(R^5)_2$ or CH=N-OA;

in I8 R^1 is $(CH_2)_nHet$ or $(CH_2)_nAr$,
R^2 is $(CH_2)_nAr$,
R^3 is H,

R^4 is $(CH_2)_nCO_2R^5$, $(CH_2)_nCO$-Het, CHO, CH_2OR^5, $(CH_2)_n$-Het, $(CH_2)_nN(R^5)_2$ or CH=N-OA,

R^5 is H, methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl or n-decyl;

in I9 R^1 is $(CH_2)_n$Het or $(CH_2)_n$Ar,

R^2 is $(CH_2)_n$Ar,

R^3 is H,

R^4 is $(CH_2)_nCO_2R^5$, $(CH_2)_nCO$-Het, CHO, CH_2OR^5, $(CH_2)_n$-Het, $(CH_2)_nN(R^5)_2$ or CH=N-OA,

R^5 is H, methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl or n-decyl,

n is 0, 1 or 2.

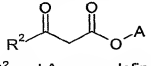
The compounds of the formula I and also the starting materials for their preparation are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can also be made here of variants which are known per se, but are not mentioned here in greater detail.

The compound of the formula III is preferably obtained by reaction of compounds of the formula V

V

in which A is as defined above,

with compounds of the formula VI



VI

in which R^2 and A are as defined above,

under conditions which are known for reactions of this type.

The starting materials can, if desired, also be formed in situ by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds of the formula I.
On the other hand, it is possible to carry out the reaction stepwise.

The starting materials of the formulae II, III and IV are generally known. If they are not known, they can be prepared by methods known per se.

Specifically, the reactions of the compounds of the formula II with the compounds of the formula III and the compounds of the formula IV are carried out in the presence or absence of a preferably inert solvent at temperatures between about -20 and about 150°, preferably between 20 and 100°.

Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents.

The pH necessary for the reaction can be set in accordance with pH values selected for similar reactions of carbonyl compounds with amino compounds. The pH is preferably pre-specified through the use of the particular acid-addition salt, preferably a hydrogen halide addition salt, of the compound of the formula II, i.e. there is no additional addition of a base or acid to the reaction mixture. Preferred acid-addition salts are hydrochlorides or hydrobromides.

A base of the formula I can be converted into the associated acid-addition salt using an acid, for example by reaction of equivalent amounts of the base and the acid in an inert solvent, such as ethanol, followed by evaporation. Suitable acids for this reaction are, in particular, those which give physiologically acceptable salts. Thus, it is possible to use inorganic acids, for example sulfuric acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as orthophosphoric acid, or sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemono- and -disulfonic acids, or laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used for the isolation and/or purification of the compounds of the formula I.

On the other hand, if desired, the free bases of the formula I can be liberated from their salts using bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate).

The invention relates in particular to compounds of the formula I and physiologically acceptable salts and solvates thereof as medicaments.

The invention also relates to the compounds of the formula I and physiologically acceptable salts and solvates thereof as glycine transporter inhibitors.

The invention furthermore relates to the use of the compounds of the formula I and/or physiologically acceptable salts and/or solvates thereof for the preparation of pharmaceutical preparations, in particular by non-chemical methods. In this case, they can be converted into a suitable dosage form together with at least one solid, liquid and/or semi-liquid

excipient or adjuvant and, if desired, in combination with one or more further active ingredients.

The invention furthermore relates to pharmaceutical preparations comprising at least one compound of the formula I and/or one of its physiologically acceptable salts and/or solvates.

These preparations can be used as medicaments in human or veterinary medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administration and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose or starch, magnesium stearate, talc or Vaseline. Suitable for oral administration are, in particular, tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops, suitable for rectal administration are suppositories, suitable for parenteral administration are solutions, preferably oil-based or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for topical application are ointments, creams or powders. The novel compounds may also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection preparations. The preparations indicated may be sterilised and/or comprise assistants, such as lubricants, preservatives, stabilisers and/or wetting agents, emulsifiers, salts for modifying the osmotic pressure, buffer substances, dyes and flavours and/or one or more further active ingredients, for example one or more vitamins.

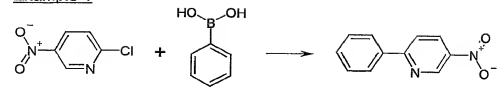
In general, the substances according to the invention are preferably administered in doses of between 1 and 500 mg, in particular between 5 and 100 mg per dosage unit.
The daily dose is preferably between about 0.02 and 10 mg/kg of body weight. However, the specific dose for each patient depends on a wide variety of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the excretion rate,

medicament combination and severity of the particular illness to which the therapy applies. Oral administration is preferred.

Above and below, all temperatures are indicated in °C. In the following examples, "conventional work-up" means that water is added if necessary, the mixture is extracted with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chromatography on silica gel and/or by crystallisation.

The glycine transporter inhibition is determined from the synaptosomal take-up of glycine. For this purpose, a synaptosomal fraction (P_2 fraction) is prepared from the brain of a rat by the method of Whittaker (The synaptosome. In: Lajtha (ed.), Handbook of Neurochemistry, Vol.2. Plenum, London and New York, 1969, 327-364), giving a synaptosome-enriched suspension of 3 mg of protein/ml. After pre-incubation of the test compounds and synaptosomes in Krebs-Ringer buffer solution (126 mmol/l of sodium chloride, 1.4 mmol/l of magnesium chloride, 4.8 mmol/l of potassium chloride, 15.8 mmol/l of disodium hydrogenphosphate, 11 mmol/l of glucose, 0.9 mmol/l of calcium chloride, pH 7.4, 346 mosmol) for 10 minutes at 37°C, ^{3}H-glycine is added, and the mixture is incubated at 37°C for a further 30 minutes. The concentration of ^{3}H-glycine is 1.75 nmol/l in a total assay volume of 575 microlitres. The non-specific take-up of glycine is determined in sodium-free Krebs-Ringer buffer solution (252 mmol/l of sucrose, 15.8 mmol/l of tris, 11 mmol/l of glucose, 1.4 mmol/l of magnesium chloride, 4.8 mmol/l of potassium chloride, 0.9 mmol/l of calcium chloride, pH 7.4, 346 mosmol).

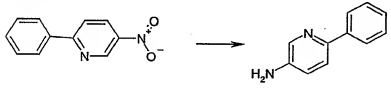
Example 1



1 2 3

A solution of 6.218 g of 1 and 1.360 g of tetrakis(triphenylphosphine)-palladium(0) in 200 ml of ethylene glycol dimethyl ether is warmed slightly and, after addition of 5.26 g of 2 and 13.107 g of caesium fluoride, is refluxed for 6 hours. Conventional work-up of the reaction mixture gives 3.

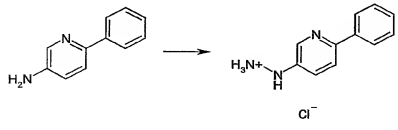
Example 2



3 4

3.02 g of 3 are hydrogenated at atmospheric pressure in the presence of 1.50 g of Raney nickel in 160 ml of methanol. Conventional work-up gives 4.

Example 3

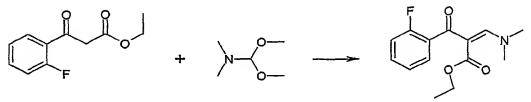


4 5

2.34 g of 4 are added to 23.3 ml of water, and 43.1 ml of 32% aqueous hydrochloric acid are added dropwise over the course of 15 minutes with stirring at from -5°C to 0°C. A solution of 0.949 g of sodium nitrite in

11.4 ml of water is subsequently added dropwise over the course of 20 minutes, and the mixture is stirred for a further 30 minutes. The resultant mixture is added dropwise at from -5°C to 0°C over the course of 20 minutes to a solution of 15.58 g of tin(II) chloride dihydrate and 35.3 ml of concentrated hydrochloric acid. The solvent is removed, and the residue is subjected to conventional work-up, giving **5**.

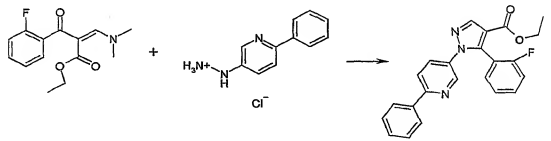
Example 4



6 **7** **8**

A solution of 41.00 ml of **6** and 61.97 ml of **7** in 820 ml of tetrahydrofuran is stirred for 80 hours and subsequently distilled, giving **8** (b.p.161°C at 0.4 mbar).

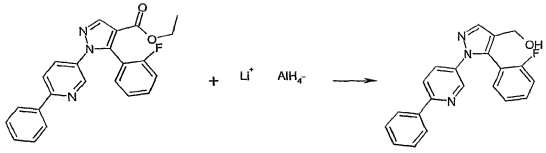
Example 5



8 **4** **9**

3.95 g of **8**, 3.30 g of **4** and 170 ml of ethanol are combined and refluxed for 5 hours. Conventional work-up of the reaction mixture gives **9**.

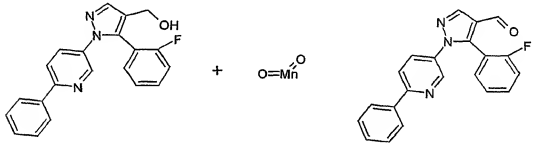
Example 6



9 **10**

A solution of 2.090 g of **9** in 25 ml of THF is added dropwise with stirring and ice cooling under a nitrogen atmosphere to a suspension of 1.139 g of lithium aluminium hydride in 25 ml of tetrahydrofuran. After the mixture has been stirred for 1 hour, a further 0.500 g of lithium aluminium hydride is added. After the mixture has been stirred for a further 2 hours, saturated sodium chloride solution is added dropwise with ice cooling, and the mixture is subjected to conventional work-up, giving **10**.

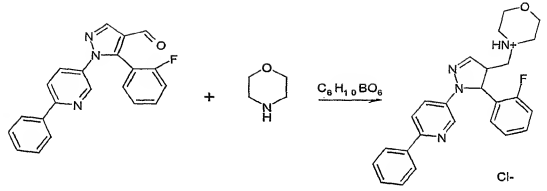
Example 7



10 **11**

1.480 g of **10**, 2.897 g of manganese(IV) oxide, 9.00 ml of tetrahydrofuran and 3.0 ml of dichloromethane are combined and stirred for 3 days. After filtration, the solvent is removed, and the residue is subjected to conventional work-up, giving **11**.

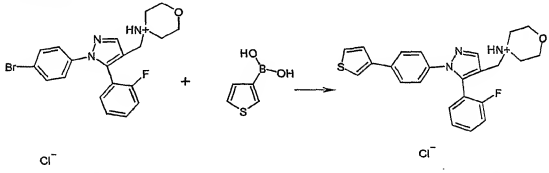
Example 8



11 **12** **13**

0.017 ml of acetic acid is added to a solution of 0.103 g of **11** and 0.040 ml of **12** in 2.00 ml of dichloroethane and 1.00 ml of tetrahydrofuran, and the mixture is stirred for 3 hours. After 0.120 g of sodium triacetoxyborohydride has been added, the mixture is stirred overnight, saturated sodium hydrogencarbonate is subsequently added, and the mixture is subjected to conventional work-up, giving **13**.

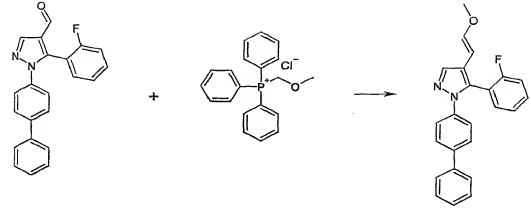
Example 9



14 **15** **16**

1.00 ml of a 2M sodium carbonate solution is added dropwise to a solution of 91.30 mg of **14**, 46.00 mg of **15** and 6.500 mg of bisdichloropalladium(II) in 3.00 ml of dimethoxyethane. The mixture is refluxed overnight. After the batch has been cooled, 5 ml of water are added, and the mixture is subjected to conventional work-up, giving **16**.

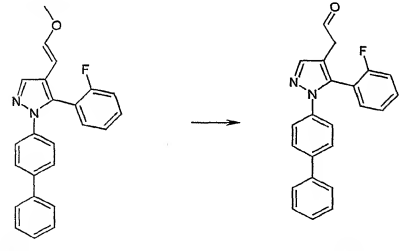
Example 10



17 **18** **19**

A solution of 0.258 g of potassium tert-butoxide in 5 ml of THF is added dropwise at a maximum of 7°C to a solution of 0.685 g of **17** and 0.789 g of **18** in 10 ml of THF with stirring and ice cooling. The reaction mixture is stirred for 2 days and subsequently subjected to conventional work-up, giving **19**.

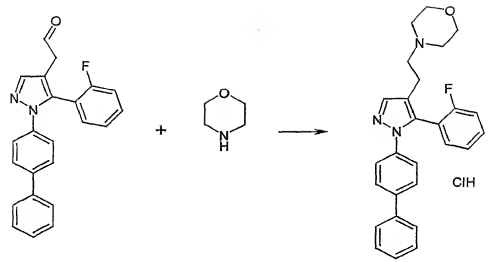
Example 11



20 **21**

A mixture of 50.00 mg of **20**, 3.00 ml of 16% aqueous sulfuric acid and 3.00 ml of toluene is refluxed for 2 hours. The mixture is subsequently stirred at room temperature for 3 days. Conventional work-up gives **21**.

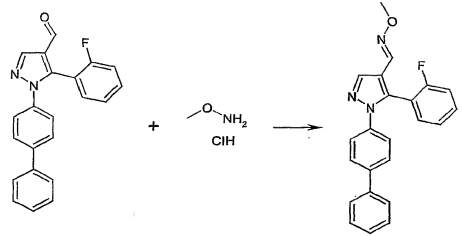
Example 12



21 **12** **22**

0.010 ml of acetic acid is added to a solution of 61.000 mg of **21** and 22.35 mg of morpholine in 3.000 ml of dichloroethane and 1.5 ml of tetrahydrofuran. The mixture is stirred for 3 hours, and 68.668 mg of sodium triacetoxyborohydride are subsequently added. After the mixture has been stirred for 2 days, it is subjected to conventional work-up, giving the free base of **22**. After reaction of the base with one equivalent of a 0.1M HCl/2-propanol solution, the hydrochloride **22** precipitates out after addition of methyl tert-butyl ether, enabling it to be isolated by filtration.

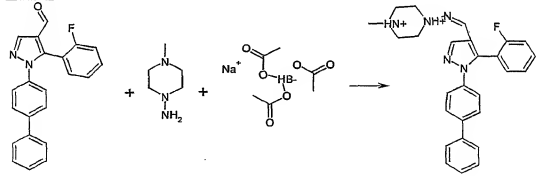
Example 13



17 23 24

0.033 ml of acetic acid is added to a solution of 200.00 mg of **17** and 74.66 mg of o-methylhydroxylamine hydrochloride **23** in 8.50 ml of dichloroethane and 4.5 ml of tetrahydrofuran, and the mixture is stirred for 3 hours. 130.287 mg of sodium triacetoxyborohydride are subsequently added. After the mixture has been stirred for 5 hours, it is subjected to conventional work-up, giving **24**.

Example 14

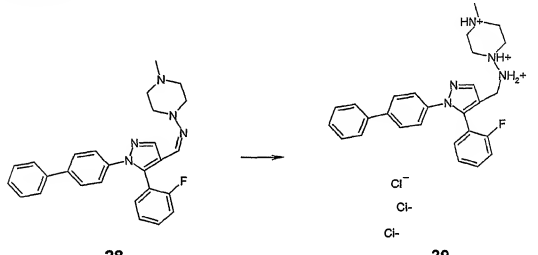


17 25 26 27

0.026 ml of acetic acid is added to 0.160 g of **17** and 0.087 ml of **25** in a mixture of 3.00 ml of dichloroethane and 1.50 ml of tetrahydrofuran, and the mixture is stirred for 3 hours.

After addition of 0.188 g of **26**, stirring is continued overnight, and the mixture is subjected to conventional work-up, giving **28**, the free base of **27**. By reaction with 1 equivalent of a 0.1M solution of HCl in 2-propanol, the hydrochloride **27** can be obtained.

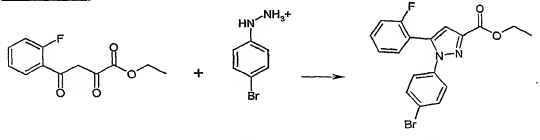
Example 15



28 **29**

80.00 mg of **28** are hydrogenated at atmospheric pressure in the presence of 0.70 g of Raney nickel in 10 ml of ethanol. Conventional work-up and addition of hydrochloric acid gives **29**.

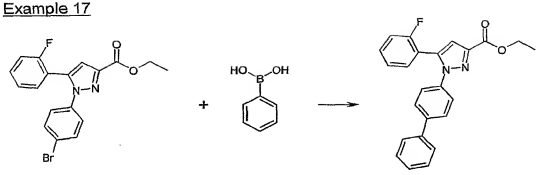
Example 16



6 **30** **31**

1.20 g of **6**, 2.70 g of **30**, 6.0 ml of hydrochloric acid and 40.0 ml of dimethylacetamide are combined and stirred overnight. After 40 ml of water have been added, the mixture is stirred for a further 4 hours and subjected to conventional work-up, giving **31**.

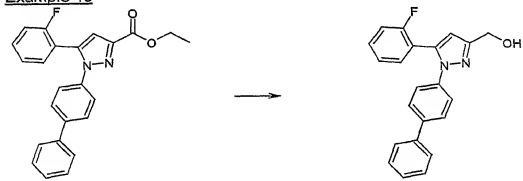
Example 17



31 **2** **32**

4.00 ml of an aqueous 2M sodium carbonate solution and 150.00 mg of tetrakis(triphenylphosphine)palladium(0) are added to a solution of 1.00 g of **31** and 630.0 mg of **2** in 15.0 ml of ethylene glycol dimethyl ether. The mixture is refluxed for 3 hours. After cooling, the mixture is subjected to conventional work-up, giving **32**.

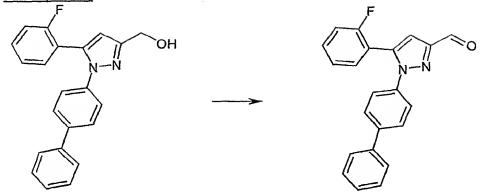
Example 18



32 **33**

A solution of 3.6 g of **32** in 30 ml of tetrahydrofuran is added dropwise in a nitrogen atmosphere to a suspension of 450.00 mg of lithium aluminium hydride in 20 ml of tetrahydrofuran. The mixture is stirred for 2 hours. 50 ml of a mixture of water and tetrahydrofuran (1:1 v/v) are slowly added dropwise with ice cooling, the resultant precipitate is filtered off with suction, and the filtrate is subjected to conventional work-up, giving **33**.

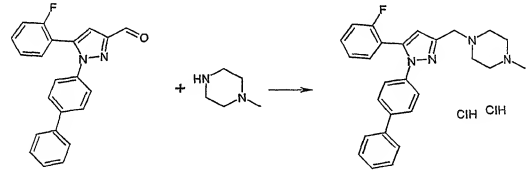
Example 19



33 34

1.600 g of **33**, 4.00 g of manganese(IV) oxide and 50.00 ml of dichloromethane are combined and stirred at room temperature for 4 hours. After a further 2 g of manganese(IV) oxide have been added, the mixture is stirred for 2 days and subsequently subjected to conventional work-up, giving **34**.

Example 20



34 35 36

0.10 ml of acetic acid is added to a solution of 430.00 mg of **34** and 0.210 ml of **35** in 10.0 ml of dichloroethane and 5.0 ml of tetrahydrofuran. The reaction mixture is stirred for 3 hours. 0.50 g of sodium triacetoborohydride is subsequently added, and the mixture is stirred for 2 hours and then subjected to conventional work-up, giving the free base of **36**, from which **36** is obtained in crystalline form by addition of ethereal HCl (m.p.: 277°C).

The following compounds according to the invention are obtained analogously using the corresponding precursors:

Examples 21 – 240:

		IC50 [mol/l]
(21)	Ethyl 1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazole-4-carbonate	
(22)	[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl]-methanol	
(23)	1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl acetate	
(24)	1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]piperidine	4.10E-7
(25)	1-Benzyl-4-[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]piperazine	4.40E-7
(26)	4-{1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]piperidin-4-yl}morpholine	1.80E-6
(27)	[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-(3-methoxypropyl)amine	1.10E-6
(28)	2-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-1,3,4,6,7,11b-hexahydro-2H-pyrazino[2,1-a]isoquinoline	1.50E-6
(29)	4-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]morpholine	3.20E-7
(30)	[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methylene]-(4-methylpiperazin-1-yl)amine	
(31)	1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-4-methylpiperazine	2.10E-7
(32)	{[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]amino}acetic acid	
(33)	tert-Butyl {[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}acetate	
(34)	1-Biphenyl-4-yl-4-(2,5-dihydropyrrol-1-ylmethyl)-5-(2-	2.50E-7

	fluorophenyl)-1H-pyrazole	
(35)	1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]azepan	9.30E-7
(36)	Benzyl-[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]ethylamine	6.00E-7
(37)	[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]diethylamine	3.30E-7
(38)	[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]dimethylamine	1.10E-6
(39)	1-Biphenyl-4-yl-5-(2-fluorophenyl)-4-pyrrolidin-1-yl-methyl-1H-pyrazole	4.70E-7
(40)	3-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]thiazolidine	1.50E-7
(41)	2-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-1,2,3,4-tetrahydroisoquinoline	5.60E-7
(42)	{1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]piperidin-4-yl}dimethylamine	8.20E-7
(43)	1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-1,2,3,6-tetrahydropyridine	2.70E-7
(44)	[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]methyl-(1-methylpiperidin-4-yl)amine	5.90E-7
(45)	4-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-2,6-dimethylmorpholine	3.80E-7
(46)	[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl](4-methylpiperazin-1-yl)amine	4.80E-6
(47)	3-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl]-acrylic acid	
(48)	1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-4-methylpiperazine	3.40E-7
(49)	Ethyl 3-[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl]acrylate	5.30E-6
(50)	3-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl]-prop-2-en-1-ol	6.30E-7
(51)	4-{2-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl]ethyl}morpholine	5.80E-7
(52)	Ethyl 1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazole-	

	3-carbonate	
(53)	[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-3-yl]-methanol	
(54)	1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-3-yl-methyl]piperidine	1.50E-6
(55)	4-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-3-yl-methyl]morpholine	3.00E-6
(56)	1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-3-yl-methyl]-4-methylpiperazine	7.70E-7
(57)	4-{3-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl]allyl}morpholine	1.60E-6
(58)	4-{3-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl]propyl}morpholine	4.40E-7
(59)	1-Biphenyl-4-yl-5-(2-fluorophenyl)-4-(2-methoxy-methylpyrrolidin-1-ylmethyl)-1H-pyrazole	8.60E-7
(60)	tert-Butyl 1-[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]pyrrolidine-2-carbonate	
(61)	tert-Butyl 2-{[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}propionate	
(62)	1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-3-(3-methoxyphenyl)piperidine	9.20E-7
(63)	1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-3-cyclohexylmethylpiperidine	
(64)	1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-4-methylpiperidine	4.00E-7
(65)	8-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-1,4-dioxa-8-azaspiro[4.5]decane	8.20E-7
(66)	tert-Butyl 2-{[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}-3-methylbutyrate	
(67)	N-{1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]pyrrolidin-3-yl}acetamide	5.80E-7
(68)	1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-2-methylpiperidine	9.40E-7
(69)	{1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]piperidin-2-ylmethyl}diethylamine	3.00E-7
(70)	Ethyl 5-(2-fluorophenyl)-1-(4-nitrophenyl)-1H-pyrazole-	

	4-carbonate	
(71)	Ethyl 1-(4-cyanophenyl)-5-(2-fluorophenyl)-1H-pyrazole-4-carbonate	
(72)	Ethyl 5-(2-fluorophenyl)-1-[4-(1H-tetrazol-5-yl)phenyl]-1H-pyrazole-4-carbonate	
(73)	1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]piperidin-4-one	4.30E-7
(74)	tert-Butyl {[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]methylamino}acetate	
(75)	1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl]-1-(4-methylpiperazin-1-yl)methanone	7.60E-7
(76)	1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]pyrrolidin-3-ol	7.60E-7
(77)	Ethyl 5-(2-fluorophenyl)-1-[4-(N-hydroxycarbamimidoyl)phenyl]-1H-pyrazole-4-carbonate	
(78)	tert-Butyl 4-[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]piperazine-1-carbonate	5.30E-6
(79)	1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]piperazine	9.20E-7
(80)	Ethyl 5-(2-fluorophenyl)-1-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]-1H-pyrazole-4-carbonate	
(81)	1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-carbaldehyde O-methyl oxime	
(82)	1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-carbaldehyde O-allyl oxime	2.80E-7
(83)	4-[1-(4'-Fluorobiphenyl-4-yl)-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]morpholine	7.00E-7
(84)	4-[5-(2-Fluorophenyl)-1-(3',4',5'-trimethoxybiphenyl-4-yl)-1H-pyrazol-4-ylmethyl]morpholine	8.70E-6
(85)	4-[5-(2-Fluorophenyl)-1-(4'-trifluoromethylbiphenyl-4-yl)-1H-pyrazol-4-ylmethyl]morpholine	6.30E-7
(86)	4'-[5-(2-Fluorophenyl)-4-morpholin-4-ylmethylpyrazol-1-yl]biphenyl-2-carbonitrile	2.20E-6
(87)	4-[1-(2'-Chlorobiphenyl-4-yl)-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]morpholine	8.40E-7
(88)	4-[1-(3',5'-Dichlorobiphenyl-4-yl)-5-(2-fluorophenyl)-	5.70E-6

	1H-pyrazol-4-ylmethyl]morpholine	
(89)	4-[5-(2-Fluorophenyl)-1-(4'-methoxybiphenyl-4-yl)-1H-pyrazol-4-ylmethyl]morpholine	1.90E-6
(90)	4-[1-(3',4'-Difluorobiphenyl-4-yl)-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]morpholine	1.10E-6
(91)	4-[5-(2-Fluorophenyl)-1-(4'-methylbiphenyl-4-yl)-1H-pyrazol-4-ylmethyl]morpholine	1.60E-6
(92)	4-[5-(2-Fluorophenyl)-1-(3'-methoxybiphenyl-4-yl)-1H-pyrazol-4-ylmethyl]morpholine	8.40E-6
(93)	4-[1-(3'-Chlorobiphenyl-4-yl)-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]morpholine	5.40E-7
(94)	4-[5-(2-Fluorophenyl)-1-(2'-trifluoromethylbiphenyl-4-yl)-1H-pyrazol-4-ylmethyl]morpholine	4.40E-6
(95)	4-[5-(2-Fluorophenyl)-1-(2'-methoxybiphenyl-4-yl)-1H-pyrazol-4-ylmethyl]morpholine	2.50E-6
(96)	4-[1-(3'-Ethoxybiphenyl-4-yl)-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]morpholine	2.10E-6
(97)	4-[1-(2'-Fluorobiphenyl-4-yl)-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]morpholine	8.90E-7
(98)	4-[1-[4-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)phenyl]-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]morpholine	1.50E-7
(99)	4-[5-(2-Fluorophenyl)-1-(4-thiophen-3-ylphenyl)-1H-pyrazol-4-ylmethyl]morpholine	1.10E-6
(100)	4-[1-(4-Butylphenyl)-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]morpholine	1.30E-6
(101)	4'-[5-(2-Fluorophenyl)-4-morpholin-4-ylmethylpyrazol-1-yl]biphenyl-4-carbonitrile	2.60E-6
(102)	4'-[5-(2-Fluorophenyl)-4-morpholin-4-ylmethylpyrazol-1-yl]biphenyl-3-carbonitrile	1.20E-6
(103)	4-[1-(3',5'-Difluorobiphenyl-4-yl)-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]morpholine	6.80E-6
(104)	4-[1-(2',4'-Difluorobiphenyl-4-yl)-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]morpholine	1.10E-6
(105)	4-[1-(2',5'-Difluorobiphenyl-4-yl)-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]morpholine	1.80E-6
(106)	4-[5-(2-Fluorophenyl)-1-(4-thiophen-2-ylphenyl)-1H-	1.90E-6

pyrazol-4-ylmethyl]morpholine

(107) 4-[1-(4'-Chlorobiphenyl-4-yl)-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]morpholine 7.50E-7

(108) 4-[5-(2-Fluorophenyl)-1-(3',4',5'-trifluorobiphenyl-4-yl)-1H-pyrazol-4-ylmethyl]morpholine 1.10E-6

(109) Ethyl 5-(2-fluorophenyl)-1-(4-trifluoromethylphenyl)-1H-pyrazole-4-carbonate

(110) 4-[5-(2-Fluorophenyl)-1-p-tolyl-1H-pyrazol-4-ylmethyl]-morpholine

(111) {[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]methylamino}acetic acid

(112) 1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]pyrrolidine-2-carboxylic acid

(113) 2-{[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}-3-methylbutyric acid

(114) 2-{[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}propionic acid

(115) 1-[1-(2'-Fluorobiphenyl-4-yl)-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]-4-methylpiperazine

(116) 1-[1-(4'-Fluorobiphenyl-4-yl)-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]-4-methylpiperazine

(117) 1-[1-(2',5'-Difluorobiphenyl-4-yl)-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]-4-methylpiperazine

(118) 1-[5-(2-Fluorophenyl)-1-(4-thiophen-3-ylphenyl)-1H-pyrazol-4-ylmethyl]-4-methylpiperazine

(119) {[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]methylamino}morpholin-4-ylethanone

(120) Ethyl 5-(2-fluorophenyl)-1-(4-imidazol-1-ylphenyl)-1H-pyrazole-4-carbonate

(121) [5-(2-Fluorophenyl)-1-(4-imidazol-1-ylphenyl)-1H-pyrazol-4-yl]methanol

(122) 1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]pyrrolidine-2-carboxamide

(123) [5-(2-Fluorophenyl)-1-(4-trifluoromethylphenyl)-1H-pyrazol-4-yl]methanol

(124) Ethyl {[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-

4-ylmethyl]amino}acetate

(125) tert-Butyl (2-{[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}ethyl)carbamate

(126) tert-Butyl 4-{[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}piperidine-1-carbonate

(127) Ethyl 1-[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]piperidine-4-carbonate

(128) Ethyl 4-{[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}piperidine-1-carbonate

(129) 4-[5-(2-Fluorophenyl)-1-(4-imidazol-1-ylphenyl)-1H-pyrazol-4-ylmethyl]morpholine

(130) 1-[5-(2-Fluorophenyl)-1-(4-imidazol-1-ylphenyl)-1H-pyrazol-4-ylmethyl]-4-methylpiperazine

(131) Ethyl {[5-(2-fluorophenyl)-1-(4-imidazol-1-ylphenyl)-1H-pyrazol-4-ylmethyl]amino}acetate

(132) Ethyl {4-[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]piperazin-1-yl}acetate

(133) 1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]piperidine-4-carboxylic acid

(134) [1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]piperidin-4-ylamine

(135) {4-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]piperazin-1-yl}acetic acid

(136) N1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]ethane-1,2-diamine

(137) {[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}acetic acid

(138) 2-{[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}ethanol

(139) [1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl](2-methoxyethyl)amine

(140) 2-{4-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]piperazin-1-yl}ethanol

(141) 1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]-4-ethylpiperidin-4-ol

(142) 1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-

methyl]-4-thiophen-3-ylpiperidin-4-ol

(143) 1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]piperidin-4-ol

(144) 5-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-2-oxa-5-azabicyclo[2.2.1]heptane

(145) 8-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-8-azabicyclo[3.2.1]octan-3-ol

(146) tert-Butyl 4-[5-(2-fluorophenyl)-1-(4-trifluoromethyl-phenyl)-1H-pyrazol-4-ylmethyl]piperazine-1-carbonate

(147) 1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]piperidine-4-carboxamide

(148) 1-[5-(2-Fluorophenyl)-1-(4-trifluoromethylphenyl)-1H-pyrazol-4-ylmethyl]piperazine

(149) 1-[5-(2-Fluorophenyl)-1-(4-trifluoromethylphenyl)-1H-pyrazol-4-ylmethyl]-4-methylpiperazine

(150) [1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl](1-ethylpyrrolidin-2-ylmethyl)amine

(151) N-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-N,N',N'-trimethylethane-1,2-diamine

(152) [1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]pyridin-3-ylmethylamine

(153) tert-Butyl 5-[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

(154) 1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-4-ethylpiperazine

(155) 1-{4-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]piperazin-1-yl}-2-pyrrolidin-1-ylethanone

(156) 2-{[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]methylamino}ethanol

(157) 4-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]piperazine-1-carbaldehyde

(158) Ethyl {1-[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]-3-oxopiperazin-2-yl}acetate

(159) 1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-4-methyl[1,4]diazepan

(160) 4-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]thiomorpholine

(161) 8-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one

(162) 1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-3,5-dimethylpiperazine

(163) [1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]pyridin-3-ylamine

(164) 1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]imidazolidin-2-one

(165) 1-[5-(2-Fluorophenyl)-1-(4-pyrrol-1-ylphenyl)-1H-pyrazol-4-ylmethyl]-4-methylpiperazine

(166) (1-Azabicyclo[2.2.2]oct-3-yl)-[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amine

(167) 4-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]thiomorpholine 1,1-dioxide

(168) 2-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane

(169) 4-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]thiomorpholine 1-oxide

(170) Ethyl 4-{[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]methylamino}piperidine-1-carboxylate

(171) Dimethyl 2-{[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}succinate

(172) 2-{4-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]piperazin-1-yl}acetamide

(173) 4-[1-(2',6'-Difluorobiphenyl-4-yl)-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]morpholine

(174) 2-{[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]amino}malonamide

(175) Ethyl [1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]carbamoylmethylcarbamate

(176) Methyl 3-{[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}propionate

(177) 4-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-

methyl]morpholine-3,5-dione

(178) 1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]piperidin-4-one O-methyl oxime

(179) 1-[5-(2-Fluorophenyl)-1-(4-isopropylphenyl)-1H-pyrazol-4-ylmethyl]-4-methylpiperazine

(180) 4-[5-(2-Fluorophenyl)-1-(4-isopropylphenyl)-1H-pyrazol-4-ylmethyl]morpholine

(181) Ethyl {[5-(2-fluorophenyl)-1-(4-isopropylphenyl)-1H-pyrazol-4-ylmethyl]amino}acetate

(182) 1-[5-(2-Fluorophenyl)-1-(4-trifluoromethoxyphenyl)-1H-pyrazol-4-ylmethyl]-4-methylpiperazine

(183) 4-[5-(2-Fluorophenyl)-1-(4-trifluoromethoxyphenyl)-1H-pyrazol-4-ylmethyl]morpholine

(184) Ethyl {[5-(2-fluorophenyl)-1-(4-trifluoromethoxyphenyl)-1H-pyrazol-4-ylmethyl]amino}acetate

(185) Ethyl 5-(2-fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazole-4-carboxylate 2.50E-6

(186) [5-(2-Fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-yl]methanol 2.30E-6

(187) 4-[5-(2-Fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]morpholine 1.20E-6

(188) tert-Butyl {[5-(2-fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]amino}acetate

(189) {[5-(2-Fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]amino}acetic acid

(190) 1-[5-(2-Fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]piperazine

(191) 1-[5-(2-Fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]-4-methylpiperazine

(192) tert-Butyl 4-[5-(2-fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]piperazine-1-carboxylate

(193) Ethyl 1-[5-(2-fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]piperidine-4-carboxylate

(194) 2-{4-[5-(2-Fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]piperazin-1-yl}nicotinonitrile

(195) tert-Butyl (2-{[5-(2-fluorophenyl)-1-(6-phenylpyridin-3-

yl)-1H-pyrazol-4-ylmethyl]amino}ethyl)carbamate

(196) tert-Butyl 4-{[5-(2-fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]amino}piperidine-1-carboxylate

(197) Methyl 5-{[5-(2-fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]amino}furan-2-carboxylate

(198) Ethyl 4-{[5-(2-fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]amino}piperidine-1-carboxylate

(199) N1-[5-(2-Fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]ethane-1,2-diamine

(200) [5-(2-Fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]piperidin-4-ylamine

(201) 1-[5-(2-Fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]piperidine-4-carboxylic acid

(202) 4-Ethyl-1-[5-(2-fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]piperidin-4-ol

(203) 5-[5-(2-Fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]-2-oxa-5-azabicyclo[2.2.1]heptane

(204) Ethyl {4-[5-(2-fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]piperazin-1-yl}acetate

(205) {4-[5-(2-Fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]piperazin-1-yl}acetic acid

(206) 5-[5-(2-Fluorophenyl)-4-piperidin-1-ylmethylpyrazol-1-yl]-2-phenylpyridine

(207) 1-{5-(2-Fluorophenyl)-1-[6-(4-fluorophenyl)pyridin-3-yl]-1H-pyrazol-4-ylmethyl}-4-methylpiperazine

(208) 4-{5-(2-Fluorophenyl)-1-[6-(4-fluorophenyl)pyridin-3-yl]-1H-pyrazol-4-ylmethyl}morpholine

(209) Ethyl ({5-(2-fluorophenyl)-1-[6-(4-fluorophenyl)pyridin-3-yl]-1H-pyrazol-4-ylmethyl}amino)acetate

(210) {[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}acetic acid

(211) tert-Butyl {[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}acetate

(212) tert-Butyl {[5-(2-fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]amino}acetate

(213) {[5-(2-Fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]amino}acetic acid

(214) tert-Butyl [(1-biphenyl-4-yl-5-phenyl-1H-pyrazol-4-ylmethyl)amino]acetate

(215) tert-Butyl {[biphenyl-4-yl-(bistrifluoromethylphenyl)-1H-pyrazol-4-ylmethyl]amino}acetate

(216) tert-Butyl 1-[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]pyrrolidine-2-carboxylate

(217) tert-Butyl 2-{[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}propionate

(218) tert-Butyl 2-{[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}-3-methylbutyrate

(219) {[Biphenyl-4-yl-(bistrifluoromethylphenyl)-1H-pyrazol-4-ylmethyl]amino}acetic acid

(220) [(1-Biphenyl-4-yl-5-phenyl-1H-pyrazol-4-ylmethyl)-amino]acetic acid

(221) tert-Butyl {[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]methylamino}acetate

(222) {[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]methylamino}acetic acid

(223) 1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]pyrrolidine-2-carboxylic acid

(224) 2-{[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]amino}-3-methylbutanoic acid

(225) 2-{[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]amino}propionic acid

(226) {[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]methylamino}morpholin-4-ylethanone

(227) 1-[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]pyrrolidine-2-carboxamide

(228) Ethyl {[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}acetate

(229) Ethyl {[5-(2-fluorophenyl)-1-(4-imidazol-1-ylphenyl)-1H-pyrazol-4-ylmethyl]amino}acetate

(230) {[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-yl-methyl]amino}acetic acid

(231) Ethyl {1-[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]-3-oxopiperazin-2-yl}acetate

(232) Dimethyl 2-{[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}succinate

(233) 2-{[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}malonamide

(234) Ethyl [1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]carbamoylmethylcarbamate

(235) Ethyl {[5-(2-fluorophenyl)-1-(4-isopropylphenyl)-1H-pyrazol-4-ylmethyl]amino}acetate

(236) Ethyl {[5-(2-fluorophenyl)-1-(4-trifluoromethoxyphenyl)-1H-pyrazol-4-ylmethyl]amino}acetate

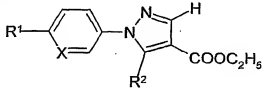
(237) Ethyl ({5-(2-fluorophenyl)-1-[6-(4-fluorophenyl)pyridin-3-yl]-1H-pyrazol-4-ylmethyl}amino)acetate

(238) Ethyl [(1-biphenyl-4-yl-5-pyridin-3-yl-1H-pyrazol-4-ylmethyl)amino]acetate

(239) 2-{[1-Biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]amino}acetamide

(240) 4-(1-Biphenyl-4-yl-5-pyridin-2-yl-1H-pyrazol-4-ylmethyl)morpholine

Examples 241 – 290:



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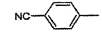
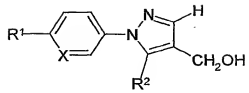
(241)			CH
(242)			CH
(243)			CH

(244)			CH
(245)			CH
(246)			CH
(247)			CH
(248)			CH
(249)			CH
(250)			CH
(251)			CH
(252)			CH
(253)			CH
(254)			CH
(255)			CH
(256)			CH
(257)			CH
(258)			CH
(259)			CH

(260)			CH
(261)		CF_3	CH
(262)		CF_3	CH
(263)		CF_3	CH
(264)		CF_3	CH
(265)		CF_3	CH
(266)			N
(267)			N
(268)			N
(269)			N
(270)			N
(271)			N
(272)			N
(273)			N
(274)			N
(275)			N
(276)			N

(277)			N
(278)			N
(279)			N
(280)			N
(281)			N
(282)			N
(283)			N
(284)			N
(285)			N
(286)		CF_3	N
(287)		CF_3	N
(288)		CF_3	N
(289)		CF_3	N
(290)		CF_3	N

Examples 291 – 340:



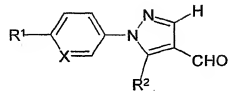
	R^1	R^2	X
(291)			CH
(292)			CH
(293)			CH
(294)			CH
(295)			CH
(296)			CH
(297)			CH
(298)			CH
(299)			CH
(300)			CH
(301)			CH
(302)			CH
(303)			CH

(304)			CH
(305)			CH
(306)			CH
(307)			CH
(308)			CH
(309)			CH
(310)			CH
(311)		CF_3	CH
(312)		CF_3	CH
(313)		CF_3	CH
(314)		CF_3	CH
(315)		CF_3	CH
(316)			N
(317)			N
(318)			N
(319)			N
(320)			N

(321)			N
(322)			N
(323)			N
(324)			N
(325)			N
(326)			N
(327)			N
(328)			N
(329)			N
(330)			N
(331)			N
(332)			N
(333)			N
(334)			N
(335)			N
(336)		CF_3	N

(337)		CF_3	N
(338)		CF_3	N
(339)		CF_3	N
(340)		CF_3	N

Examples 341 – 390:



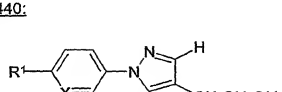
	R^1	R^2	X
(341)			CH
(342)			CH
(343)			CH
(344)			CH
(345)			CH
(346)			CH
(347)			CH
(348)			CH

(349)			CH
(350)			CH
(351)			CH
(352)			CH
(353)			CH
(354)			CH
(355)			CH
(356)			CH
(357)			CH
(358)			CH
(359)			CH
(360)			CH
(361)		CF_3	CH
(362)		CF_3	CH
(363)		CF_3	CH
(364)		CF_3	CH

(365)		CF_3	CH
(366)			N
(367)			N
(368)			N
(369)			N
(370)			N
(371)			N
(372)			N
(373)			N
(374)			N
(375)			N
(376)			N
(377)			N
(378)			N
(379)			N
(380)			N

(381)			N
(382)			N
(383)			N
(384)			N
(385)			N
(386)		CF_3	N
(387)		CF_3	N
(388)		CF_3	N
(389)		CF_3	N
(390)		CF_3	N

Examples 391 – 440:



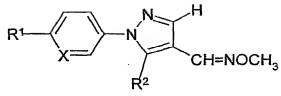
	R^1	R^2	X
(391)			CH
(392)			CH
(393)			CH

(394)			CH
(395)			CH
(396)			CH
(397)			CH
(398)			CH
(399)			CH
(400)			CH
(401)			CH
(402)			CH
(403)			CH
(404)			CH
(405)			CH
(406)			CH
(407)			CH
(408)			CH
(409)			CH

(410)			CH
(411)		CF_3	CH
(412)		CF_3	CH
(413)		CF_3	CH
(414)		CF_3	CH
(415)		CF_3	CH
(416)			N
(417)			N
(418)			N
(419)			N
(420)			N
(421)			N
(422)			N
(423)			N
(424)			N
(425)			N
(426)			N

(427)			N
(428)			N
(429)			N
(430)			N
(431)			N
(432)			N
(433)			N
(434)			N
(435)			N
(436)		CF_3	N
(437)		CF_3	N
(438)		CF_3	N
(439)		CF_3	N
(440)		CF_3	N

Examples 441 – 490:



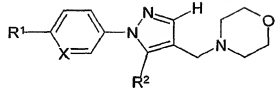
	R^1	R^2	X
(441)			CH
(442)			CH
(443)			CH
(444)			CH
(445)			CH
(446)			CH
(447)			CH
(448)			CH
(449)			CH
(450)			CH
(451)			CH
(452)			CH

	(453)			CH
	(454)			CH
	(455)			CH
	(456)			CH
	(457)			CH
	(458)			CH
	(459)			CH
	(460)			CH
	(461)		CF_3	CH
	(462)		CF_3	CH
	(463)		CF_3	CH
	(464)		CF_3	CH
	(465)		CF_3	CH
	(466)			N
	(467)			N
	(468)			N
	(469)			N

(470)			N
(471)			N
(472)			N
(473)			N
(474)			N
(475)			N
(476)			N
(477)			N
(478)			N
(479)			N
(480)			N
(481)			N
(482)			N
(483)			N
(484)			N
(485)			N

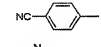
(486)		CF_3	N
(487)		CF_3	N
(488)		CF_3	N
(489)		CF_3	N
(490)		CF_3	N

Examples 491 – 540:



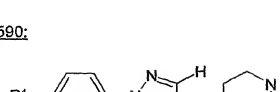
	R^1	R^2	X
(491)			CH
(492)			CH
(493)			CH
(494)			CH
(495)			CH
(496)			CH
(497)			CH

(498)			CH
(499)			CH
(500)			CH
(501)			CH
(502)			CH
(503)			CH
(504)			CH
(505)			CH
(506)			CH
(507)			CH
(508)			CH
(509)			CH
(510)			CH
(511)		CF_3	CH
(512)		CF_3	CH
(513)		CF_3	CH

(514)		CF_3	CH
(515)		CF_3	CH
(516)			N
(517)			N
(518)			N
(519)			N
(520)			N
(521)			N
(522)			N
(523)			N
(524)			N
(525)			N
(526)			N
(527)			N
(528)			N
(529)			N

(530)			N
(531)			N
(532)			N
(533)			N
(534)			N
(535)			N
(536)		CF_3	N
(537)		CF_3	N
(538)		CF_3	N
(539)		CF_3	N
(540)		CF_3	N

Examples 541 – 590:



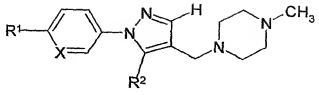
	R^1	R^2	X
(541)			CH

(542)			CH
(543)			CH
(544)			CH
(545)			CH
(546)			CH
(547)			CH
(548)			CH
(549)			CH
(550)			CH
(551)			CH
(552)			CH
(553)			CH
(554)			CH
(555)			CH
(556)			CH
(557)			CH

(558)			CH
(559)			CH
(560)			CH
(561)		CF_3	CH
(562)		CF_3	CH
(563)		CF_3	CH
(564)		CF_3	CH
(565)		CF_3	CH
(566)			N
(567)			N
(568)			N
(569)			N
(570)			N
(571)			N
(572)			N
(573)			N
(574)			N

(575)			N
(576)			N
(577)			N
(578)			N
(579)			N
(580)			N
(581)			N
(582)			N
(583)			N
(584)			N
(585)			N
(586)		CF_3	N
(587)		CF_3	N
(588)		CF_3	N
(589)		CF_3	N
(590)		CF_3	N

Examples 591 – 640:



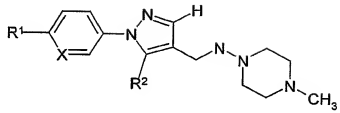
	R^1	R^2	X
(591)			CH
(592)			CH
(593)			CH
(594)			CH
(595)			CH
(596)			CH
(597)			CH
(598)			CH
(599)			CH
(600)			CH
(601)			CH
(602)			CH

(603)			CH
(604)			CH
(605)			CH
(606)			CH
(607)			CH
(608)			CH
(609)			CH
(610)			CH
(611)		CF_3	CH
(612)		CF_3	CH
(613)		CF_3	CH
(614)		CF_3	CH
(615)		CF_3	CH
(616)			N
(617)			N
(618)			N
(619)			N

(620)			N
(621)			N
(622)			N
(623)			N
(624)			N
(625)			N
(626)			N
(627)			N
(628)			N
(629)			N
(630)			N
(631)			N
(632)			N
(633)			N
(634)			N
(635)			N

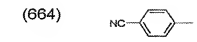
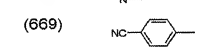
(636)		CF_3	N
(637)		CF_3	N
(638)		CF_3	N
(639)		CF_3	N
(640)		CF_3	N

Examples 641 – 690:



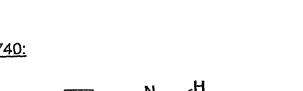
	R^1	R^2	X
(641)			CH
(642)			CH
(643)			CH
(644)			CH
(645)			CH
(646)			CH
(647)			CH

(648)			CH
(649)			CH
(650)			CH
(651)			CH
(652)			CH
(653)			CH
(654)			CH
(655)			CH
(656)			CH
(657)			CH
(658)			CH
(659)			CH
(660)			CH
(661)		CF_3	CH
(662)		CF_3	CH
(663)		CF_3	CH

(664)		CF_3	CH
(665)		CF_3	CH
(666)			N
(667)			N
(668)			N
(669)			N
(670)			N
(671)			N
(672)			N
(673)			N
(674)			N
(675)			N
(676)			N
(677)			N
(678)			N
(679)			N

(680)			N
(681)			N
(682)			N
(683)			N
(684)			N
(685)			N
(686)		CF_3	N
(687)		CF_3	N
(688)		CF_3	N
(689)		CF_3	N
(690)		CF_3	N

Examples 691 – 740:



	R^1	R^2	X
(691)			CH

(692)			CH
(693)			CH
(694)			CH
(695)			CH
(696)			CH
(697)			CH
(698)			CH
(699)			CH
(700)			CH
(701)			CH
(702)			CH
(703)			CH
(704)			CH
(705)			CH
(706)			CH
(707)			CH

(708)			CH
(709)			CH
(710)			CH
(711)		CF_3	CH
(712)		CF_3	CH
(713)		CF_3	CH
(714)		CF_3	CH
(715)		CF_3	CH
(716)			N
(717)			N
(718)			N
(719)			N
(720)			N
(721)			N
(722)			N
(723)			N
(724)			N

(725)			N
(726)			N
(727)			N
(728)			N
(729)			N
(730)			N
(731)			N
(732)			N
(733)			N
(734)			N
(735)			N
(736)		CF_3	N
(737)		CF_3	N
(738)		CF_3	N
(739)		CF_3	N
(740)		CF_3	N

The examples below relate to pharmaceutical preparations:

Example A: Injection vials

A solution of 100 g of an active ingredient of the formula I and 5 g of disodium hydrogenphosphate in 3 l of bidistilled water is adjusted to pH 6.5 using 2N hydrochloric acid, sterile filtered, transferred into injection vials, lyophilised under sterile conditions and sealed under sterile conditions. Each injection vial contains 5 mg of active ingredient.

Example B: Suppositories

A mixture of 20 g of an active ingredient of the formula I is melted with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active ingredient.

Example C: Solution

A solution is prepared from 1 g of an active ingredient of the formula I, 9.38 g of $NaH_2PO_4 \cdot 2\ H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12\ H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilised by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

500 mg of an active ingredient of the formula I are mixed with 99.5 g of Vaseline under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of active ingredient of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed in a conventional manner to give tablets in such a way that each tablet contains 10 mg of active ingredient.

Example F: Coated tablets

Tablets are pressed analogously to Example E and subsequently coated in a conventional manner with a coating of sucrose, potato starch, talc, tragacanth and dye.

Example G: Capsules

2 kg of active ingredient of the formula I are introduced in a conventional manner into hard gelatine capsules in such a way that each capsule contains 20 mg of the active ingredient.

Example H: Ampoules

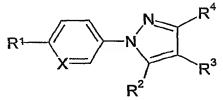
A solution of 1 kg of active ingredient of the formula I in 60 l of bidistilled water is sterile filtered, transferred into ampoules, lyophilised under sterile conditions and sealed under sterile conditions. Each ampoule contains 10 mg of active ingredient.

Example I: Inhalation spray

14 g of active ingredient of the formula I are dissolved in 10 l of isotonic NaCl solution, and the solution is transferred into commercially available spray containers with pump mechanism. The solution can be sprayed into the mouth or nose. One spray shot (about 0.1 ml) corresponds to a dose of about 0.14 mg.

Patent Claims

1. Compounds of the formula I



I

in which

X is CH or N,

R^1 is H, A, Hal, $(CH_2)_nHet$, $(CH_2)_nAr$, cycloalkyl having from 3 to 7 carbon atoms, CF_3, NO_2, CN, C(NH)NOH or OCF_3,

R^2 is $(CH_2)_nHet$, $(CH_2)_nAr$, cycloalkyl having from 3 to 7 carbon atoms or CF_3,

R^3 and R^4 are H, $(CH_2)_nCO_2R^5$, $(CH_2)_nCOHet$, $(CH_2)_nCOO(CH_2)_nHet$, CHO, $(CH_2)_nOR^5$, $(CH_2)_nHet$, $(CH_2)_nN(R^5)_2$, CH=N-OA, CH_2CH=N-OA, $(CH_2)_nNHOA$, $(CH_2)_nN(R^5)Het$, $(CH_2)_nCH$=N-Het, $(CH_2)_nOCOR^5$, $(CH_2)_nN(R^5)CH_2CH_2OR^5$, $(CH_2)_nN(R^5)CH_2CH_2OCF_3$, $(CH_2)_nN(R^5)C(R^5)HCOOR^5$, $(CH_2)_nN(R^5)CH_2COHet$, $(CH_2)_nN(R^5)CH_2Het$, $(CH_2)_nN(R^5)CH_2CH_2Het$, $(CH_2)_nN(R^5)CH_2CH_2N(R^5)CH_2COOR^5$, $(CH_2)_nN(R^5)CH_2CH_2N(R^5)_2$, CH=$CHCOOR^5$, CH=$CHCH_2NR^5Het$, CH=$CHCH_2N(R^5)_2$, CH=$CHCH_2OR^5$, $(CH_2)_nN(R^5)Ar$, $(CH_2)_nN(COOR^5)COOR^5$, $(CH_2)_nN(CONH_2)COOR^5$, $(CH_2)_nN(CONH_2)CONH_2$, $(CH_2)_nN(CH_2COOR^5)COOR^5$, $(CH_2)_nN(CH_2CONH_2)COOR^5$, $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^5COR^5$, $(CH_2)_nCHR^5COOR^5$ or $(CH_2)_nCHR^5CH_2OR^5$, where in each case one of the radicals R^3 or R^4 is H,

R^5 is H or A,

A is straight-chain or branched alkyl having from 1 to 10 carbon atoms, alkenyl having from 2 to 10 carbon atoms or alkoxyalkyl having from 2 to 10 carbon atoms,

Het is a saturated, unsaturated or aromatic monocyclic or bicyclic heterocyclic radical which is unsubstituted or monosubstituted or polysubstituted by A and/or Hal,

Ar is a phenyl radical which is unsubstituted or monosubstituted or [polysubstituted by A and/or Hal, OR^5, $OOCR^5$, $COOR^5$, $CON(R^5)_2$, CN, NO_2, NH_2, CF_3 or SO_2CH_3,

n is 0, 1, 2, 3, 4 or 5,

and

Hal is F, Cl, Br or I,

and salts and solvates thereof,

where compounds of the formula I in which R^1 and R^4 are H, X is CH_2, R^2 is phenyl or p-chlorophenyl, and R^3 is 1-methyl-4-piperidyloxycarbonyl, 2-(4-phenylpiperazino)ethoxycarbonyl, benzoxazol-2-yl, benzothiazol-2-yl, tetrazol-5-yl or unsubstituted or substituted thiazolidin-2-yl, and salts and solvates thereof, are excluded.

2. Compounds of the formula I according to Claim 1, in which R^1 is phenyl, 2-, 3- or 4-cyanophenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-methyl-, -ethyl-, -n-propyl- or -n-butylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4-, 3,5- or 3,6-difluoro-, -dichloro- or -dicyanophenyl, 3,4,5-trifluorophenyl, 3,4,5-trimethoxy- or -triethoxyphenyl, thiophen-2-yl or thiophen-3-yl.

3. Compounds of the formula I according to one or more of the preceding claims, in which R^3 is H.

4. Compounds of the formula I according to one or more of the preceding claims, in which R^4 is H.

5. Compounds of the formula I according to one or more of the preceding claims, in which R^2 is phenyl, 2-, 3- or 4-cyanophenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-methyl-, -ethyl-, -n-propyl- or -n-butylphenyl, 2,3-, 2,4-, 2,5- or 2,6-difluoro- or -dicyanophenyl, thiophen-2-yl or thiophen-3-yl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, quinolinyl, isoquinolinyl, 2- or 4-pyridazyl, 2-, 4- or 5-pyrimidyl, or 2- or 3-pyrazinyl.

6. Compounds of the formula I according to one or more of the preceding claims, in which X is CH.

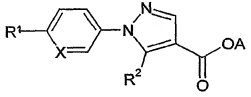
7. Compounds of the formulae (a) to (j) according to Claim 1:
   (a) 1-biphenyl-4-yl-4-(2,5-dihydropyrrol-1-ylmethyl)-5-(2-fluorophenyl)-1H-pyrazole
   (b) 1-[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]-1,2,3,6-tetrahydropyridine
   (c) 1-[1-biphenyl-4-yl-5-(2-fluorophenyl)-1H-pyrazol-4-ylmethyl]-4-methylpiperazine
   (d) 1-[5-(2-fluorophenyl)-1-(6-phenylpyridin-3-yl)-1H-pyrazol-4-ylmethyl]-4-methylpiperazine
   (e) {5-(2-Fluoro-phenyl)-1-[6-(4-fluoro-phenyl)-pyridin-3-yl]-1H-pyrazol-4-ylmethyl}-isoxazol-3-yl-amine
   (f) [5-(2-Fluoro-phenyl)-1-(6-phenyl-pyridin-3-yl)-1H-pyrazol-4-ylmethyl]-pyridin-3-yl-amine
   (g) [5-(2-Fluoro-phenyl)-1-(6-phenyl-pyridin-3-yl)-1H-pyrazol-4-ylmethyl]-isoxazol-3-yl-amine
   (h) {5-(2-Fluoro-phenyl)-1-[6-(4-fluoro-phenyl)-pyridin-3-yl]-1H-pyrazol-4-ylmethyl}-pyridin-3-yl-amine

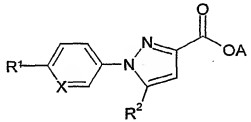
(i) [5-(2-Fluoro-phenyl)-1-(6-phenyl-pyridin-3-yl)-1H-pyrazol-4-ylmethyl]-pyrazin-2-yl-amine

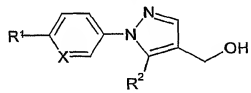
(j) {5-(2-Fluoro-phenyl)-1-[6-(4-fluoro-phenyl)-pyridin-3-yl]-1H-pyrazol-4-ylmethyl}-pyrazin-2-yl-amine

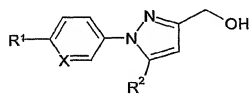
and salts and solvates thereof.

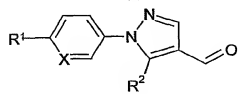
8. Compounds of the formulae IA, IB, IC, ID, IE and IF:

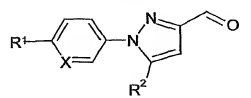

IA


IB


IC


ID

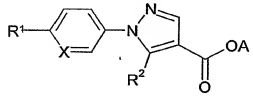

IE


IF

in which

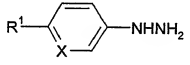
R^1, R^2 and X are as defined in Claim 1.

9. Process for the preparation of compounds of the formula IA



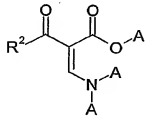
IA

in which R^1, R^2, R^3, R^4, X and A are as defined in Claim 1, and salts and solvates thereof, which is characterised in that a compound of the formula II



II

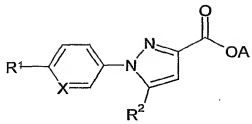
or acid-addition salts thereof
in which
R^1 and X are as defined in Claim 1,
is reacted with a compound of the formula III



III

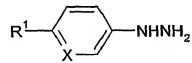
in which
A and R^2 are as defined in Claim 1,
and/or in that a basic compound of the formula IA is converted into one of its salts by treatment with an acid.

10. Process for the preparation of compounds of the formula IB



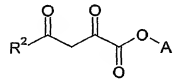
IB

in which R^1, R^2, R^3, R^4, X and A are as defined in Claim 1,
and salts and solvates thereof, which is characterised in that a compound of the formula II



II

or acid-addition salts thereof
in which
R^1 and X are as defined in Claim 1,
is reacted with a compound of the formula IV



IV

in which
A and R^2 are as defined in Claim 1,
and/or in that a basic compound of the formula IB is converted into one of its salts by treatment with an acid.

11. Compounds of the formula I according to Claim 1 and physiologically acceptable salts and solvates thereof as medicaments.

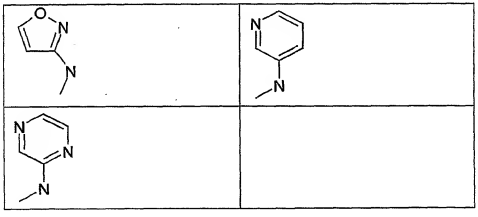
12. Compounds of the formula I according to Claim 1 and physiologically acceptable salts and solvates thereof as glycine transporter inhibitors.

13. Pharmaceutical preparation, characterised by a content of at least one compound of the formula I according to Claim 1 and/or one of its physiologically acceptable salts and/or one of its solvates.

14. Process for the preparation of pharmaceutical preparations, characterised in that a compound of the formula I according to Claim 1 and/or one of its physiologically acceptable salts and/or one of its solvates is converted into a suitable dosage form together with at least one solid, liquid or semi-liquid excipient or adjuvant.

15. Use of compounds of the formula I according to Claim 1 and/or physiologically acceptable salts or solvates thereof for the preparation of a medicament for the prophylaxis and/or treatment of schizophrenia, depression, dementia, Parkinson's disease, Alzheimer's disease, Lewy bodies dementia, Huntington's disease, Tourette's syndrome, anxiety, learning and memory restrictions, neurodegenerative disorders and other cognitive impairments, as well as nicotine dependence and pain.

16. Compounds of the formula I in which Het is one of the following radicals:



INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 02/10172

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/06 C07D231/12 C07D231/14 C07D401/14 A61K31/415
A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 27394 A (GLEN ROBERT ;MADGE DAVID (GB); SELWOOD DAVID (GB); UNIV LONDON (GB) 18 May 2000 (2000-05-18)	2-16
X	* see formulae (Ia), (Va), preparation example 18 *	1

A	US 6 001 854 A (BORDEN LAURENCE A ET AL) 14 December 1999 (1999-12-14) the whole document	1-16

A	EP 0 014 847 A (MERCK PATENT GMBH) 3 September 1980 (1980-09-03) claim 1	1-16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 January 2003	23/01/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lauro, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 57024 A (SELWOOD DAVID ;UNIV LONDON (GB); WISHART GRANT (GB); KLING MARCEL) 9 August 2001 (2001-08-09) claim 1 ---	1-16
P,A	WO 01 87855 A (MERCK PATENT GMBH ;ARLT MICHAEL (DE); GREINER HARTMUT (DE); MAENO) 22 November 2001 (2001-11-22) abstract; examples ---	1-16
X	KUDO N ET AL: "SYNTHESIS AND HERBICIDAL ACTIVITY OF 1,5-DIARYLPYRAZOLE DERIVATIVES" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 47, no. 6, 1999, pages 857-868, XP001026111 ISSN: 0009-2363 * see compounds 16 b,d,e,f,i,j,l,m,n,o,s * ---	1
X	J. BECK; F. WRIGHT: "Synthesis of 1-aryl5-(trifluoromethyl)-1H-prazole-4-carboxylic acids and esters" J. HETEROCYCLIC CHEM., vol. 24, 1987, pages 739-740, XP002226574 * see compounds 2a, 2c, 3a, 3c * ---	1
X	G. MENOZZI ET AL.: "Synthesis of 5-substituted 1-aryl-1H-pyrazole-4-acetonitriles, 4-methyl-1-phenyl-1H-pyrazole-3-carbonitriles and pharmacologically acive 1-aryl1H-pyrazole-4-acetic acids" J. HETEROCYCLIC CHEM., vol. 30, 1993, pages 997-1002, XP002226575 * see compounds I, II, V * ---	1
X	G. MENOZZI ET AL.: "Reaction of 2-dimethylaminomethylene-1,3-diones with dinucleophiles" J. HETEROCYCLIC CHEM., vol. 24, 1987, pages 1669-75, XP002226576 * see compounds III f-g, IV f-g * ---	1
X	F. CORELLI ET AL.: "Heterocyclic systems. VIII. Synthesis of 1H,4H-Pyrazolo'4,3-f!pyrrolo'1,2-a!azepine derivatives" J. HETEROCYCLIC CHEM., vol. 24, 1987, pages 1445-7, XP002226577 examples 5-9 --- -/--	1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CANNON G W ET AL: "ACYLATION STUDIES. I. METHYL CYCLOPROPYL KETONE" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 17, no. 5, 1 May 1952 (1952-05-01), pages 685-692, XP000573850 ISSN: 0022-3263 example VIII	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/10172

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty of the formula (I) as defined in claim 1. So many documents were retrieved that the search Authority decided to cite in the Search Report only a sample of the documents found during the search carried out on the basis of the definition of formula (I) as given in claim 1. The search is to be considered complete as regards the definition of formula (I) wherein R1 has the meaning as specified in claim 2 (i.e. wherein R1 represents a phenyl or a heteroaryl group), which also supports all the examples as claimed in claim 7.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/EP 02/10172

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0027394	A	18-05-2000	AU	6481699 A	29-05-2000
			WO	0027394 A1	18-05-2000
US 6001854	A	14-12-1999	NONE		
EP 0014847	A	03-09-1980	DE	2906252 A1	28-08-1980
			AU	5556280 A	28-08-1980
			EP	0014847 A1	03-09-1980
			ES	8102120 A1	01-04-1981
			JP	55120583 A	17-09-1980
			US	4258047 A	24-03-1981
			ZA	8000922 A	25-02-1981
WO 0157024	A	09-08-2001	AU	3200201 A	14-08-2001
			EP	1252156 A1	30-10-2002
			WO	0157024 A1	09-08-2001
WO 0187855	A	22-11-2001	AU	5676901 A	26-11-2001
			WO	0187855 A1	22-11-2001